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DOCKET NO: C1039.70021US01

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Krieg et al.

Serial No:

Confirmation No:

Not yet assigned Not yet assigned

Filed:

Herewith

For:

METHODS OF TREATING CANCER USING

IMMUNOSTIMULATORY OLIGONUCLEOTIDES

Examiner:

Art Unit:

Not yet assigned

Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

# STATEMENT FILED PURSUANT TO THE DUTY OF DISCLOSURE UNDER 37 CFR §§1.56, 1.97 AND 1.98

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. §§1.56, 1.97 and 1.98, the Applicant requests consideration of this Information Disclosure Statement.

# Compliance with 37 C.F.R. §1.97

This Information Disclosure Statement has been filed

before the mailing date of a first Office Action on the merits in the above-identified case.

No fee or certification is required.

### Information Cited

The Applicant hereby makes of record in the above-identified application the information listed on the attached form PTO-1449 (modified). The order of presentation of the references should not be construed as an indication of the importance of the references.

#### Remarks

Documents cited anywhere in the Information Disclosure Statement are enclosed unless otherwise indicated. It is respectfully requested that:

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- 1. The Examiner consider completely the cited information, along with any other information, in reaching a determination concerning the patentability of the present claims;
- 2. The enclosed form PTO-1449 be signed by the Examiner to evidence that the cited information has been fully considered by the Patent and Trademark Office during the examination of this application;
  - 3. The citations for the information be printed on any patent which issues from this application.

By submitting this Information Disclosure Statement, the Applicant makes no representation that a search has been performed, of the extent of any search performed, or that more relevant information does not exist.

By submitting this Information Disclosure Statement, the Applicant makes no representation that the information cited in the Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. §1.56(b).

By submitting this Information Disclosure Statement, the Applicant makes no representation that the information cited in the Statement is, or is considered to be, in fact, prior art as defined by 35 U.S.C. §102.

Notwithstanding any statements by the Applicant, the Examiner is urged to form his own conclusion regarding the relevance of the cited information.

An early and favorable action is hereby requested.

Respectfully submitted, Krieg et al., Applicant

Rv

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**XNDDX** 

#### APPLICATION NO.: Not yet assigned FORM PTO-1449/A and B (Modified) ATTY. DOCKET NO.: C1039.70021US01 INFORMATION DISCLOSURE FILING DATE: Herewith CONFIRMATION NO.: Not yet assigned STATEMENT BY APPLICANT APPLICANT: Krieg et al. GROUP ART UNIT: Not yet assigned **EXAMINER:** of 10 Sheet 1

U.S. PATENT DOCUMENTS

| Examiner's | Cite | U.S. Patent Docum | nent         | Name of Patentee or Applicant of Cited | Date of Publication or of issue |
|------------|------|-------------------|--------------|--|---------------------------------|
| Initials   | No.  | Number            | Kind<br>Code | Document                               | of Cited Document<br>MM-DD-YYYY |
|            | *    | 3,906,092         |              | Hilleman et al.                        | 09/16/75                        |
|            | *    | 5,417,972         |              | Bhat et al.                            | 05/23/95                        |
|            | *    | 5,248,670         |              | Draper et al.                          | 09/28/93                        |
|            | *    | 5,445,938         |              | Hanai et al.                           | 08/29/95                        |
|            | *    | 5,491,088         |              | Hellstrom et al.                       | 02/13/96                        |
|            | *    | 5,585,479         |              | Hoke et al.                            | 12/17/96                        |
|            | *    | 5,663,153         |              | Hutcherson et al.                      | 09/02/97                        |
|            | *    | 5,679,647         |              | Carson et al.                          | 10/21/97                        |
|            | *    | 5,723,335         |              | Hutcherson et al.                      | 03/03/98                        |
|            | *    | 5,756,097         |              | Landucci et al.                        | 05/26/98                        |
|            | *    | 5,780,448         |              | Davis                                  | 07/14/98                        |
|            | *    | 5,786,189         |              | Locht et al.                           | 07/28/98                        |
|            | *    | 5,837,243         |              | Deo et al.                             | 11/17/98                        |
|            | *    | 5,849,719         |              | Carson et al.                          | 12/15/98                        |
|            | *    | 6,426,334         |              | Agrawal et al.                         | 07/30/02                        |

FOREIGN PATENT DOCUMENTS

| Examiner's | Cite | Foreign Patent Document |             |              | Name of Patentee or Applicant of Cited | Date of Publication of       | Translation |
|------------|------|-------------------------|-------------|--------------|--|------------------------------|-------------|
| Initials   | No.  | Office/<br>Country      | Number      | Kind<br>Code | Document (not necessary)               | Cited Document<br>MM-DD-YYYY | ent (Y/N)   |
|            | *    |                         | WO 91/12811 |              |  | 09/05/91                     |             |
|            | *    | EPO                     | 0468520 A3  |              |  | 01/29/92                     |             |
|            | *    |                         | WO 92/03456 |              |  | 03/05/92                     |             |
|            | *    |                         | WO 92/18522 |              |  | 10/29/92                     |             |
|            | *    |                         | WO 92/21353 |              |  | 12/10/92                     |             |
|            | *    | EPO                     | 0302758 81  |              |  | 03/16/94                     |             |
|            | *    |                         | WO 94/19945 |              |  | 09/15/94                     |             |
|            | *    |                         | WO 95/05853 |              |  | 03/02/95                     |             |
|            | *    |                         | WO 95/26204 |              |  | 10/95                        |             |
|            | *    |                         | WO 96/02555 |              |  | 02/01/96                     |             |
|            | *    |                         | WO 96/02560 |              |  | 02/0196                      |             |
|            | *    |                         | WO 96/35782 |              |  | 11/14/96                     |             |
|            | *    |                         | WO 97/28259 |              |  | 08/07/97                     |             |
|            | *    |                         | WO 98/14210 |              |  | 04/09/98                     |             |
|            | *    |                         | WO 98/18810 |              |  | 05/07/98                     |             |
|            | *    |                         | WO 98/32462 |              |  | 07/30/98                     |             |
|            | *    |                         | WO 98/37919 |              |  | 09/03/98                     |             |
|            | *    |                         | WO 98/40100 |              |  | 09/17/98                     | <u> </u>    |
|            | *    |                         | WO 98/52581 |              |  | 11/26/98                     |             |
|            | *    |                         | WO 98/55495 |              |  | 12/10/98                     |             |

| FORM PTO | )-1449/A and B (M | lodifie | d)     | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
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|          | RMATION D         |         |        | FILING DATE:     | Herewith         | CONFIRMATION NO.: Not yet assigned |
| STAT     | EMENT BY          | APP     | LICANT | APPLICANT:       | Krieg et al.     |                                    |
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| Examiner's<br>Initials | Cite<br>No | Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s), publisher, city and/or country where published. | Translation<br>(Y/N) |
|------------------------|------------|---|----------------------|
|                        | *          | Adya N et al., Expansion of CREB's DNA recognition specificity by Tax results from interaction with Ala-Ala-Arg at positions 282-284 near the conserved DNA-binding domain of CREB. <i>Proc Natl Acad Sci USA</i> 91(12):5642-6, 7 Jun 1994.                            |                      |
|                        | *          | AGGARWAL, S.K. et al., "Cell-Surface-Associated Nucleic Acid in Tumorigenic Cells Made Visible with Platinum-Complexes by Electron Microscopy", <i>Proc. Nat. Acad. Sci. USA</i> , March 1975, Pages 928-932, Vol. 72, No. 3  |                      |
|                        | *          | Angier, N., Microbe DNA Seen as Alien By Immune System, New York Times, 4/11/95   |                      |
|                        | *          | Azad RF et al., Antiviral Activity of a Phosphorothioate Oligonucleotide Complementary to RNA of the Human Cytomegalovirus Major Immediate-Early Region. <i>Antimicrobial Agents and Chemotherapy</i> , 37:1945-1954, September, 1993.                                  |                      |
|                        | *          | Azuma, Biochemical and Immunological Studies on Cellular Components of Tubercle Bacilli, Kekkaku, Vol. 69, 9:45-55, 1992.   |                      |
|                        | *          | Ballas ZK et al., Induction of NK activity in murine and human cells by CpG motifs in oligodeoxynucleotides and bacterial DNA. <i>J Immunol</i> 157(5):1840-5, 1996.  |                      |
|                        | *          | Bayever, E., Systemic Administration of a Phosphorothioate Oligonucleotide with a Sequence Complementary to p53 for Acute Myelogenous leukemia and Myelodysplastic Syndrome: Initial Results of a Phase I Trial, <i>Antisense Res. &amp; Dev.</i> (1993), 3:383-390.    |                      |
|                        | *          | Bennett RM et al., DNA binding to human leukocytes. Evidence for a receptor-mediated association, internalization, and degradation of DNA. <i>J Clin Invest</i> 76(6):2182-90, 1985.  |                      |
|                        | *          | Berg DJ et al., Interleukin-10 is a central regulator of the response to LPS in murine models of endotoxic shock and the Shwartzman reaction but not endotoxin tolerance. <i>J Clin Invest</i> 96(5):2339-47, 1995.   |                      |
|                        | *          | Bernhard, M., et al., "Monocyte Macrophage Mediated Antibody Depedent and Independent Cell Mediated Cytotoxicity in Normals and Cancer Patients, ABSTRACT, <i>Proceedings of AACR and ASCO</i> , 22:372, c-159  |                      |
|                        | *          | Blanchard DK et al., Interferon-gamma induction by lipopolysaccharide: dependence on interleukin 2 and macrophages. <i>J Immunol</i> 136(3):963-70, 1986.   |                      |
|                        | *          | Blaxter et al., Genes expressed in Brugia malayi infective third stage larvae. <i>Molecular and Biochemical Parasitology</i> , 77:77-93.  |                      |
|                        | *          | Boggs RT et al., Characterization and modulation of immune stimulation by modified oligonucleotides. <i>Antisense Nucleic Acid Drug Dev</i> 7(5):461-71, Oct 1997.  |                      |
|                        | *          | Branda RF et al., Amplification of antibody production by phosphorothioate oligodeoxynucleotides.  J. Lab Clin Med 128(3):329-38, Sep 1996.   |                      |

| FORM PTO | )-1449/A and B (M | odifie | d)     | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
|----------|-------------------|--------|--------|------------------|------------------|------------------------------------|
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| Examiner's<br>Initials | Cite<br>No | Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s), publisher, city and/or country where published. | Translation<br>(Y/N) |
|------------------------|------------|---|----------------------|
|                        | *          | Branda et al., Immune Stimulation by an Antisense Oligomer Complementary to the rev gene of HIV-1. <i>Biochemical Pharmacology</i> , Vol. 45, 10:2037-2043, 1993.   |                      |
|                        | *          | Briskin M et al., Lipopolysaccharide-unresponsive mutant pre-B-cell lines blocked in NF-kappa B activation. <i>Mol Cell Biol</i> 10(1):422-5, Jan 1990.   |                      |
|                        | *          | Chace, J. et al., Regulation of Differentiation in CD5+ and Conventional B Cells, Clinical Immunology and Immunopathology, (1993), 68:3:327-332.  |                      |
|                        | *          | Chang YN et al., The palindromic series I repeats in the simian cytomegalovirus major immediate-<br>early promoter behave as both strong basal enhancers and cyclic AMP response elements. <i>J Virol</i> 64(1):264-77, Jan 1990.                                       |                      |
|                        | *          | Chu RS et al., CpG oligodeoxynucleotides act as adjuvants that switch on T helper 1 (Th1) immunity.<br>J Exp Med 186(10):1623-31, 17 Nov 1997.  |                      |
|                        | *          | Cohen, J., et al., "IL-12 Deaths: Explanation and a Puzzle", Science, 10:270:5238:908   |                      |
|                        | *          | Cossum, P., et al., "Pharmacokinetics of a <sup>14</sup> C-Labeled Phosphorothioate Oligonucleotide, ISIS 2105, after Intradermal Administration to Rats", The Journal of Pharmacology and Experimental Therapeutics, 269:1:89-94, (1993)                               |                      |
|                        | *          | Cowdery JS et al., Bacterial DNA induces NK cells to produce IFN-gamma in vivo and increases the toxicity of lipopolysaccharides. <i>J Immunol</i> 156(12):4570-5, 15 Jun 1996.   |                      |
|                        | *          | Crosby et al., The Early Responses Gene FGFI-C Encodes a Zinc Finger Transcriptional Activator and is a Member of the GCGGGGGCG (GSG) Element-Binding Protein Family. <i>Mol. Cell. Biol.</i> , 2:3835-3841, 1991.  |                      |
|                        | *          | Crystal, Transfer of Genes to Humans: Early Lessons and Obstacles to Success. <i>Science</i> , Vol. 270, pp. 404-410, 1995.   |                      |
|                        | *          | D'Andrea A et al., Interleukin 10 (IL-10) inhibits human lymphocyte interferon gamma-production by suppressing natural killer cell stimulatory factor/IL-12 synthesis in accessory cells. <i>J Exp Med</i> 178(3):1041-8, 1993.   |                      |
|                        | *          | Doe, B., et al., "Induction of cytotoxic T lymphocytes by intramuscular immunization with plasmid DNA is faciliated by bone marrow-derived cells", <i>Proc. Natl. Acad. Sci.</i> , 93:8578-8583, (1996)   |                      |
|                        | *          | Englisch et al., Chemically Modified Oligonucleotides as Probes and Inhibitors, <i>Angew. Chem. Int. Ed. Engl.</i> , 30:613-629, 1991.  |                      |
|                        | *          | Erb KJ et al., Infection of mice with Mycobacterium bovis-Bacillus Calmette-Guerin (BCG) suppresses allergen- induced airway eosinophilia. <i>J Exp Med</i> 187(4):561-9, 16 Feb 1998.  |                      |
|                        | *          | Etlinjer, Carrier sequence selection - one key to successful vaccines, <i>Immunology Today</i> , Vol. 13, 2:52-55, 1992.  |                      |
|                        | *          | Fox RI, Mechanism of action of hydroxychloroquine as an antirheumatic drug. <i>Chemical Abstracts</i> , 120:15, Abstract No. 182630 (April 29, 1994).   |                      |
|                        | *          | Gately, M., et al., "Interleukin-12: A Recently Discovered Cytokine with potential for Enhancing Cell-Mediated Immune Responses to Tumors", Cancer Investigation, 11:4:500-506, (1993)  |                      |

| FORM PTC | )-1449/A and B (M | lodifie | d)     | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
|----------|-------------------|---------|--------|------------------|------------------|------------------------------------|
|          | RMATION D         |         |        | FILING DATE:     | Herewith         | CONFIRMATION NO.: Not yet assigned |
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| Examiner's Initials | Cite<br>No | Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s),   | Translation (Y/N) |
|---------------------|------------|---|-------------------|
|                     |            | publisher, city and/or country where published.   | (3,7,7)           |
|                     | *          | Gura, T., Antisense Has Growing Pains. Science (1995), 270:575-576.   |                   |
|                     | *          | Hadden J et al., Immunostimulants. TIPS, (1993), 141:169-174.   |                   |
|                     | *          | Hadden J et al., Immunopharmacology, JAMA, (1992) 268:20:2964-2969.   |                   |
|                     | *          | Halpern MD et al., Bacterial DNA induces murine interferon-gamma production by stimulation of interleukin-12 and tumor necrosis factor-alpha. <i>Cell Immunol</i> 167(1):72-8, 1996.  |                   |
|                     | *          | Hamblin, T., et al., "Ex Vivo Acitivation and Retransfusion of White Blood Cells", Curr Stud Hematol Blood Transf., 57:249-266, (1990)  |                   |
|                     | *          | Hartmann, G., et al., "CpG DNA: A potent signal for growth, activation, and maturation of human dendritic cells", <i>Proc. Natl. Acad. Sci.</i> , 96:9305-9310, (1999)  |                   |
|                     | *          | Hatzfeld J., Release of Early Human Hematopoietic Progenitors from Quiescence by Antisense Transforming Growth Factor β1 or Rb Oligonucleotides, J. Exp. Med., (1991) 174:925-929.  |                   |
|                     | *          | Highfield PE, Sepsis: the More, the Murkier. <i>Biotechnology</i> , 12:828, August 12, 1994.  |                   |
| 11.1.1011           | *          | Hoeffler JP et al., Identification of multiple nuclear factors that interact with cyclic adenosine 3',5'-monophosphate response element-binding protein and activating transcription factor-2 by protein-protein interactions. <i>Mol Endocrinol</i> 5(2):256-66, Feb 1991.         |                   |
|                     | *          | Iguchi-Ariga SM and Shaffner W, CpG methylation of the cAMP-responsive enhancer/promoter sequence TGACGTCA abolishes specific factor binding as well as transcriptional activation. <i>Genes Dev</i> 3(5):612-9, May 1989.  |                   |
|                     | *          | Iverson, P., et al., "Pharmacokinetics of an Antisense Phosphorothioate Oligodeoxynucleotide against reve from Human Immunodeficiency Virus Type 1 in the Adult male Rate Following Single Injections and Continuous Infusion", Antisense Research and Development, (1994), 4:43-52 |                   |
|                     | *          | Ishikawa R et al., IFN induction and associated changes in splenic leukocyte distribution. <i>J Immunol</i> 150(9):3713-27, 1 May 1993  |                   |
|                     | *          | Jakway JP et al., Growth regulation of the B lymphoma cell line WEHI-231 by anti-immunoglobulin, lipopolysaccharide, and other bacterial products. <i>J Immunol</i> 137(7):2225-31, 1 Oct 1986.   |                   |
|                     | *          | Jaroszewski JW and Cohen JS, Cellular uptake of antisense oligonucleotides. <i>Adv Drug Delivery Rev</i> 6(3):235-50, 1991.   |                   |
|                     | *          | Kataoka, T., et al. "Immunotherapeutid potential in Guinea-Pig Tumor Model of Deoxyribonucleic Acid From Mycobacterium Bovix BCG Complexed with Poly-L-Lysine and Carboxy-Methylcellulose", <i>Jpn J. Med. Sci. Biol.</i> 43:171-182, (1990)  |                   |
| 1,000               | *          | KATAOKA, T. et al., "Antitumor Activity of Synthetic Oligonucleotides with Sequences from cDNA Encoding Proteins of <i>Mycobacterium bovis</i> BCG", <i>Jpn. J. Cancer Res.</i> , March 1992, Pages 244-247, Vol. 83  |                   |
|                     | *          | Kimura Y et al., Binding of Oligoguanylate to Scavenger Receptors Is Required for Oligonucleotides to Augment NK Cell Activity and Induce IFN, J. Biochem., Vol. 116, 5:991-994, 1994.  |                   |

| FORM PTO | D-1449/A and B (M | odifie | d)      | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
|----------|-------------------|--------|---------|------------------|------------------|------------------------------------|
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| Examiner's<br>Initials | Cite<br>No | Include name of the author (in CAPITAL LETTERS) title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, relevant page(s), volume-issue number(s). publisher, city and/or country where published. | Translation<br>(Y/N) |
|------------------------|------------|---|----------------------|
|                        | *          | Kline JN et al., CpG motif oligonucleotides are effective in prevention of eosinophilic inflammation in a murine model of asthma. <i>J Invest Med</i> 44(7):380A, 1996.   |                      |
|                        | *          | Kline JN et al., Immune redirection by CpG oligonucleotides. Conversion of a Th2 response to a Th1 response in a murine model of asthma. <i>J Invest Med</i> 45(3):282A, 1997.  |                      |
|                        | *          | Kline JN et al., CpG oligonucleotides can reverse as well as prevent Th2-mediated inflammation in a murine model of asthma. <i>J Invest Med</i> 45(7):298A, 1997.   |                      |
|                        | *          | Klinman DM et al., CpG motifs present in bacteria DNA rapidly induce lymphocytes to secrete interleukin 6, interleukin 12, and interferon gamma. <i>Proc Natl Acad Sci USA</i> 93(7):2879-83, 1996.   |                      |
|                        | *          | KLINMAN, D.M. et al., "Contribution of CpG Motifs to the Immunogenicity of DNA Vaccines", J. of Immunol., 1997, Pages 3635-3639, Vol. 158, No. 8, The American Association of Immunologists   |                      |
|                        | *          | Kolitz, J., et al., "The Immunotherapy of Human Cancer with Interleukin 2: Present Status and Future Directions", Cancer Investigation, 9:5:529-542, (1991)   |                      |
|                        | *          | Krieg AM, An innate immune defense mechanism based on the recognition of CpG motifs in microbial DNA. <i>J Lab Clin Med</i> 128(2):128-33, 1996.  |                      |
| *                      | *          | Krieg AM et al., Uptake of oligodeoxyribonucleotides by lymphoid cells is heterogeneous and inducible. <i>Antisense Res Dev</i> 1(2):161-71, Summer 1991.   |                      |
|                        | *          | Krieg AM et al., Oligodeoxynucleotide modifications determine the magnitude of B cell stimulation by CpG motifs. <i>Antisense Nucleic Acid Drug Dev</i> 6(2):133-9, Summer 1996.  |                      |
|                        | *          | Krieg AM et al., "Modification of antisense phosphodiester oligodeoxynucleotides by a 5' cholesteryl moiety increases cellular association and improves efficacy", <i>Proc. Natl. Acad. Sci.</i> , (1993), 90:1048-1052   |                      |
|                        | *          | Krieg AM et al., "CpG DNA: A Pathogenic Factor in Systemic Lupus Erythematosus?", Journal of Clinical Immunology, (1995) 15:6:284-292   |                      |
|                        | *          | Krieg AM et al, "Phosphorothioate Oligodeoxynucleotides: Antisense or Anti-Protein?, Antisense Research and Development, (1995), 5:241  |                      |
|                        | *          | Krieg AM et al., "Leukocyte Stimulation by Oligodeoxynucleotides", Applied Antisense Oligonucleotide Technology, (1998), 431-448  |                      |
|                        | *          | Krieg AM et al., CpG motifs in bacterial DNA trigger direct B-cell activation. <i>Nature</i> 374:546-9, 1995.   |                      |
|                        | *          | Krieg AM et al, "The role of CpG dinuleotides in DNA vaccines", Trends in Microbiology, Vol. 6, pp. 23-27, Jan 1998.  |                      |
|                        | *          | Krieg AM el al, "A Role for Endogenous Retroviral Sequences in the Regulation of Lymphocyte Activation, the Journal of Immunology, Vol. 143, 2448-2451,   |                      |
|                        | *          | Kuramoto et al., "Oligonucleotide Sequences Required for Natural Killer Cell Activation, <i>Jpn. J. Cancer Res.</i> , 83:1128-1131, November 1992.  |                      |
|                        | *          | Kuramoto et al., "In Situ Infiltration of Natural Killer-Like Cell sInduced by Intradermal Injection of the Nucleic Injection of the Nucleic Acid Fraction from BCG", <i>Microbiol. Immunol.</i> , 33:11:929-940, (1989)  |                      |

| FORM PTO | 0-1449/A and B (M | odifie | d)     | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
|----------|-------------------|--------|--------|------------------|------------------|------------------------------------|
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|---|------------|---|-------------------|
|   | *          | publisher, city and/or country where published.  Kuramoto, E., et al., "Changes of host cell infiltration into meth a fibrosarcoma tumor during the course of regression induced by injections of a BCG nucleic acid fraction", Int. I. Immunopharmacol. 14:5:773-782, (1992) |                   |
|   | *          | Lacour, J., et al., "Clinical Trials Using Polyadenylic-Polyuridylic Acid as an Adjuvant to Surgery in Treating Different Human Tumors, <i>J of Biological Response Modifiers</i> , 4:538-543, (1985)   |                   |
|   | *          | Leonard et al., Conformation of Guanine 8-Oxoadenine Base Pairs in the Crystal Structure of d(CGCGAATT(08A)GCG). <i>Biochemistry</i> , 31(36):8415-8420, 1992.  |                   |
|   | *          | LIPFORD, G.B. et al., "CpG-containing synthetic oligonucleotides promote B and cytotoxic T cell responses to protein antigen: a new class of vaccine adjuvants", Eur. J. Immunol., 1997, Pages 2340-2344, Vol. 27   |                   |
|   | *          | LIPFORD, G.B. et al, "Bacterial DNA as immune cell activator", Inst. of Med. Microb., Immunol. and Hygiene, 1998, Pages 496-500, Elsevier Science   |                   |
| 1                                       | *          | Macfarlane DE and Manzel L, Antagonism of immunostimulatory CpG-oligodeoxynucleotides by quinacrine, chloroquine, and structurally related compounds. <i>J Immunol</i> 160(3):1122-31, Feb 1 1998.  |                   |
|   | *          | Mastrangelo et al. Seminars in Oncology. Vol. 23, 1:4-21, 1996.   |                   |
| ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | *          | Mashiba, H., et al., "In Vitro Augmentation of Natural Killer Activity of Peripheral Bllod Cells From Cancer Patients by a DNA Fraction From Mycobacterium Bovis BCG", <i>Jpn J. Med. Sci. Biol.</i> , 41:197-202, (1988)   |                   |
|   | *          | Matson S and Krieg AM, Nonspecific suppression of [3H]thymidine incorporation by "control" oligonucleotides. <i>Antisense Res Dev</i> 2(4):325-30, Winter 1992.   |                   |
|   | *          | McIntyre KW et al., A sense phosphorothioate oligonucleotide directed to the initiation codon of transcription factor NF-kappa B p65 causes sequence-specific immune stimulation. <i>Antisense Res Dev</i> 3(4):309-22, Winter 1993.  |                   |
|   | *          | Messina et al., The Influence of DNA Structure on the <i>in vitro</i> Stimulation of Murine Lymphocytes by Natural and Synthetic Polynucleotide Antigens. <i>Cellular Immunology</i> , 147:148-157, 1993.   |                   |
|   | *          | Messina et al., Stimulation of <i>in vitro</i> Murine Lymphocyte Proliferation by Bacterial DNA. <i>J. Immunol.</i> , Vol. 147, 6:1759-1764, September 15, 1991.  |                   |
|   | *          | Mojcik, C., et al., "Administration of a Phosphorothioate Oligonucleotide Antisense Murine Endogenous Retroviral MCF env Causes Immune Effect in vivo in a Sequence-Specific Manner", Clinical Immunology and Immunopathology, (1993), 67:2:130-136                           |                   |
|   | *          | Morahan, P., et al., "Comparative Analysis of Modulators of Nonspecific Resistance Against Microbial Infections", Immunopharmacology of Infectious Diseases: Vaccine Adjuvants and Modulators of Non-Specific Resistance, 313-324, (1987)                                     |                   |
|   | *          | Mottram et al., A novel CDC2-related protein kinase from leishmania mexicana LmmCRK1 is post-translationally regulated during the life cycle. <i>J. Biol. Chem.</i> 268:28, 21044-21052 (October 1993).   |                   |
|   | *          | New England BIOLABS 1988-1989 Catalog   |                   |
|   | *          | Nyce JW and Metzger WJ, DNA antisense therapy for asthma in an animal model. <i>Nature</i> 385:721-725, 20 Feb 1997.  |                   |

| FORM PTC               | )-1449/A and B (M | lodifie         | d)               | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
|------------------------|-------------------|-----------------|------------------|------------------|------------------|------------------------------------|
|                        | RMATION I         |                 |                  | FILING DATE:     | Herewith         | CONFIRMATION NO.: Not yet assigned |
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|------------------------|------------|---|--|--|--|--|
|                        | *          | Pisetsky, D., "Stimulation of in vitro proliferation of murine lymphocytes by synthetic oligodeoxynucleotides", Molecular Biology Repairs, (1993) 18:217-221  |  |  |  |  |
|                        | *          | Pisetsky et al., Stimulation of Murine Lymphocyte Proliferation by a Phosphorothioate Oligonucleotide with Antisense Activity for Herpes Simplex Virus. <i>Life Science</i> , Vol. 54, pp. 101-107 (1994).  |  |  |  |  |
|                        | *          | Pisetsky, The Immunological Properties of DNA, <i>The Journal of Immunology</i> , pp. 421-423 (1996).   |  |  |  |  |
|                        | *          | Pisetsky, Immunological Consequences of Nucleic Acid Therapy, Antisense Research and Development, 5:219-225 (1995).   |  |  |  |  |
|                        | *          | Raz E et al., Preferential induction of a Th1 immune response and inhibition of specific IgE antibody formation by plasmid DNA immunization. <i>Proc Natl Acad Sci USA</i> 93(10):5141-5, 14 May 1996.  |  |  |  |  |
|                        | *          | Reisfeld, R., et al., "Monoclonal Antibodies in Cancer Therapy", Clinics in Laboratory Medicine, 12:2:201-216, (1992)   |  |  |  |  |
|                        | *          | Rosenberg, S., et al., "Immunotherapy of Cancer by Systemic Administration of Lymphoid Cells Plus Interleukin-2", Journal of Biological Response Modifiers, 3:501-511, (1984)-  |  |  |  |  |
|                        | *          | Rosenberg, S., et al., "Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukins-2 to patients with metastatic cancer", The New England Journal of Medicine, 113:23:1485-1492, (1985)                   |  |  |  |  |
|                        | *          | Roman M et al., Immunostimulatory DNA sequences function as T helper-1-promoting adjuvants.  Nat Med 3(8):849-54, Aug 1997.   |  |  |  |  |
|                        | *          | Sato et al., Immunostimulatory DNA Sequences Necessary for Effective Intradermal Gene Immunization, <i>Science</i> , Vol. 273, pp. 352-354, 1996.   |  |  |  |  |
|                        | *          | Schnell et al., Identification and characterization of a Saccharomyces cerevisiae gene (PAR1) conferring resistance to iron chelators. <i>Eur. J. Biochem.</i> , 200:487-493.   |  |  |  |  |
|                        | *          | Schwartz DA et al., Endotoxin responsiveness and grain dust-induced inflammation in the lower respiratory tract. <i>Am J Physiol</i> 267(5 Pt 1):L609-17, 1994.   |  |  |  |  |
|                        | *          | Schwartz DA et al., The role of endotoxin in grain dust-induced lung disease. Am J Respir Crit Care Med 152(2):603-8, 1995.   |  |  |  |  |
|                        | *          | Schwartz DA et al., CpG motifs in bacterial DNA cause inflammation in the lower respiratory tract. J Clin Invest 100(1):68-73, 1 Jul 1997.  |  |  |  |  |
|                        | *          | Shimada, S., et al., "In Vivo Augmentatio of Natural Killer Cell Activity With A Deoxyribonucleic Acid Fraction of BCG", Jpn J. Cancer Res., 77:808-816, (1986)   |  |  |  |  |
|                        | *          | Shimada, S., et al., "Antitumor Acitivity of the DNA Fraction from Mycobacterium bovis BCG. II> Effects on Various Syngeneic Mouse Tumors", JNCI, 74:3:681-688, (1985)  |  |  |  |  |
|                        | *          | Shirakawa T et al., The inverse association between tuberculin responses and atopic disorder. <i>Science</i> 275(5296):77-9, 3 Jan 1997.  |  |  |  |  |
|                        | *          | Sparwasser T et al., Macrophages sense pathogens via DNA motifs: induction of tumor necrosis factor-alpha-mediated shock. <i>Eur J Immunol</i> 27(7):1671-9, Jul 1997.  |  |  |  |  |
|                        | *          | Stein CA et al., Oligonucleotides as inhibitors of gene expression: a review. Cancer Research, 48:2659-2668, 1988.  |  |  |  |  |

| FORM PTO               | )-1449/A and B (M | 1odifie         | d)               | APPLICATION NO.: | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |  |
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|------------------------|------------|---|----------------------|
|                        | *          | Stevenson, H., et al., "The Treatment of Cancer with Activated Cytotoxic Leukocyte Subsets", Artif Organs, 12:2:128136, 1988  |                      |
|                        | *          | Stull et al., Antigene, Ribozyme, and Aptamer Nucleic Acid Drugs: Progress and Prospects, <i>Pharmaceutical Res.</i> , Vol. 12, 4:465-483, 1995.  |                      |
|                        | *          | Subramanian et al., Theoretical Considerations on the "Spine of Hydration" in the Minor Groove of d(CGCGAATTCGCG) d(GCGCTTAAGCGC): Monte Carlo Computer Simulation. <i>Proc. Nat'l. Acad. Sci. USA</i> , 85:1836-1840, 1988.  |                      |
|                        | *          | Tanaka T et al., An antisense Oligonucleotide complementary to a sequence in IG2b increases G2b germline transcripts stimulates B cell DNA synthesis and inhibits immunoglobulin secretion. <i>J. Exp. Med.</i> , 175:597-607, 1992.                                    |                      |
|                        | *          | THREADGILL, D.S. et al., "Mitogenic synthetic polynucleotides suppress the antibody response to a bacterial polysaccharide", <i>Vaccine</i> , 1998, Pages 76-82, Vol. 16, No. I, Elsevier Science Ltd.  |                      |
|                        | *          | Thorne PS., Experimental grain dust atmospheres generated by wet and dry aerosolization techniques. Am J Ind Med 25(1):109-12, 1994.  |                      |
|                        | *          | Tokunaga T et al., Synthetic Oligonucleotides with Particular Base Sequences form the cDNA Encoding Proteins of <i>Myobacterium bovis</i> BCG Induce Interferons and Activate Natural Killer Cells, <i>Microbiol. Immunol.</i> , Vol. 36, 1:55-66, 1992.                |                      |
|                        | *          | Tokunaga et al., A Synthetic Single-Stranded DNA, Ply (dG, dC), Induces Interferon α/β and -γ, Augments Natural Killer Activity and Suppresses Tumor Growth. <i>Jpn. J. Cancer Res.</i> , 79:682-686, June 1988.  |                      |
|                        | *          | Topalian, S., et al., "Expansion of human tumor infiltrating lymphocytes for use in immunotherapy trials", J of Immunological Methods, 102:127-141, (1987)  |                      |
|                        | *          | Torpey III, D., et al., "Effects of Adoptive Immunotherapy with Autologous CD8+ t Lymphocytes on Immunologic Parameters: Lymphocyte Subsets and Cytotoxic Activity, <i>Clinical Immunology and Immunopathology</i> , 68:3:263-272, (1993)                               |                      |
|                        | *          | Uhlmann et al., Antisense Oligonucleotides: A New Therapeutic Principle. Chemical Reviews, 90:543-584, 1990.  |                      |
|                        | *          | Vogels, M., et al., "Use of Immune Modulators in nonspecific Therapy of Bacterial Infections", Antimicrobial Agents and Chemotherapy, 36:1:1-5, (1992)  |                      |
|                        | *          | Wagner RW, Gene inhibition using antisense oligodeoxynucleotides. <i>Nature</i> , 372:L333-335, 1994.   |                      |
|                        | *          | Wallace et al., Oligonucleotide probes for the screening of recombinant DNA libraries. <i>Methods in Enzymology</i> , 152:432-442 (1987).   |                      |
|                        | *          | Weiss R., Upping the Antisense Ante: Scientists bet on profits from reverse genetics. Science, 139:108-109, 1991.   |                      |
|                        | *          | Whalen R, DNA Vaccines for Emerging Infection Diseases: What If?, Emerging Infectious Disease, Vol. 2, 3:168-175, 1996.   |                      |
|                        | *          | Wooldridge, J., et al., "Immunostimulatory Oligodeoxynucleotides Containing CpG Motifs Enhance the Efficacy of Monoclonal Antibody Therapy of Lymhoma", <i>Blood</i> , 89:8:2994-2998, (1997)   |                      |

| FORM PTO               | O-1449/A and B (M | lodifie | :d) | APPLICATION NO.:                     | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
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|                        | *          | WILTROUT, R.H., et al., "Immunomodulation of Natural Killer Activity by Polyribonucleotides",<br>Journal of Biological Response Modifiers, 1985, Pages 512-517, Vol. 4, No. 5, New Raven Press, NY   |                      |
|                        | *          | WOOLDRIDGE, J.E. et al., "Select Unmethylated CpG Oligodeoxynucleotides Improve Antibody Dependent Cellular Cytotoxicity in Vitro of Both Murine and Human B Cell Lymphomas", Blood, December 1995, Page 2877, Abstract, Vol. 86   |                      |
|                        | *          | WOOLDRIDGE, J.E. et al., "Select unmethylated CpG oligodeoxynucleotide improve antibody dependent cellular cytotoxicity <i>in vitro</i> and <i>in vivo</i> ", Proceedings of the American Association for Cancer Research #3253, March 1996, Page 477, Abstract, Vol. 37 |                      |
|                        | *          | Wu GY et al., Receptor-mediated gene delivery and expression in vivo. J. Biol. Chem., 263:14621-14624, 1988.   |                      |
|                        | *          | Wu-Pong S., Oligonucleotides: Opportunities for Drug Therapy and Research. <i>Pharmaceutical Technology</i> , 18:102-114, 1994.  |                      |
|                        | *          | Yamamoto S et al., DNA from bacteria, but not from vertebrates, induces interferons, activates natural killer cells and inhibits tumor growth. <i>Microbiol Immunol</i> 36(9):983-97, 1992.  |                      |
|                        | *          | Yamamoto S et al., <i>In vitro</i> augmentation of natural killer cell activity and production of interferonalpha/beta and -gamma with deoxyribonucleic acid fraction from <i>Mycobacterium bovis</i> BCG. <i>Jpn J Cancer Res</i> 79:866-73, Jul 1988.                  |                      |
|                        | *          | Yamamoto S., Mode of Action of Oligonucleotide Fraction Extracted from Mycobacterium bovis BCG, Kekkaku, Vol. 69, 9:29-32, 1994.   |                      |
|                        | *          | Yamamoto S et al., Unique Palindromic Sequences in Synthetic Oligonucleotides are Required to Induce INF and Augment INF-Mediated Natural Killer Activity. <i>J. Immunol.</i> , Vol. 148, 12:4072-4076, June 15, 1992.   |                      |
|                        | *          | Yamamoto T et al., Ability of Oligonucleotides with Certain Palindromes to Induce Interferon Production and Augment Natural Killer Cell Activity is Associated with Their Base Length.  Antisense Res. and Devel., 4:119-123, 1994.                                      |                      |
|                        | *          | Yamamoto et al., Lipofection of Synthetic Oligodeoxyribonucleotide Having a Palindromic Sequence AACGTT to Murine Splenocytes Enhances Interferon Production and Natural Killer Activity. <i>Microbiol. Immunol.</i> , Vol. 38, 10:831-836, 1994.                        |                      |
|                        | *          | Yamamoto T et al., Synthetic Oligonucleotides with Certain Palindromes Stimulate Interferon Production of Human Peripheral Blood Lymphocytes in vitro. Jpn. J. Cancer Res., 85:775-779, 1994.  |                      |
|                        | *          | Yi, Ae-Kyung et al., IFN-y Promotes IL-6 and IgM Secretion in Response to CpG Motifs in Bacterial DNA and Oligonucleotides, <i>The Journal of Immunology</i> , pp. 558-564 (1996).   |                      |
|                        | *          | Yi, Ae-Kyung et al., Rapid Immune Activation by CpG Motifs in Bacterial DNA, <i>The Journal of Immunology</i> , pp. 5394-5402 (1996).  |                      |

| FORM PTO-1449/A and B (Modified) |           |                |         | APPLICATION NO.:                      | Not yet assigned | ATTY. DOCKET NO.: C1039.70021US01  |
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|            |      | publisher, city and/or country where published.   | ,            |
|            | *    | Zhao Q et al., Stage-specific oligonucleotide uptake in murine bone marrow B-cell precursors. <i>Blood</i> 84(11):3660-6, 1 Dec 1994. |              |
|            | *    | Zhao Q et al., Comparison of cellular binding and uptake of antisense phosphodiester,   | <del> </del> |
|            | :    | phosphorothioate, and mixed phosphorothioate and methylphosphonate oligonucleotides. <i>Antisense</i>                                 |              |

| EXAMINER | DATE CONSIDERED |
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Res Dev 3(1):53-66, Spring 1993.

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